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Characterization of Cellular Responses to Stent Materials

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Background: The material composition of drug-eluting stents (DES), such as polymers and metals, may contribute to the acute and chronic biological responses associated with stent implantation. In contrast to stents having a conformal polymer coating, the Synergy stent offers a luminal platinum chromium (PtCr) surface exposed to blood and vascular cells. This study characterizes the relative cellular responses to PtCr and a stent polymer (PVDF-HFP), including endothelialization, platelet adhesion, and inflammation, in light of the relative levels of protein absorption to these surfaces.
Methods: Human coronary artery endothelial cell (HCAEC) coverage and function were examined via an on-stent ELISA and IHC staining, respectively. Protein absorption to surfaces was detected through the use of specific antibodies. Human monocyte secretion of IL-8, IL-1β, and TNF-α upon 24-hour exposure to surfaces characterized inflammatory potential. Platelet adhesion was measured under flow conditions.
Results: HCAEC coverage of PtCr stents was significantly greater than PVDF-HFP-coated stents at 7 and 14 days. Expression of VE-Cadherin, ZO-1, and eNOS appeared greater on PtCr than on PVDF-HFP, whereas Thrombomodulin levels appeared similar on the two materials. Platelet adhesion was observed on average to be less on PtCr, compared to PVDF. Inflammatory cytokine secretion was not different between the two materials. While both materials absorbed similar amount of vitronectin and fibrinogen, PtCr showed a preferential binding of fibronectin (40-50% greater) compared to PVDF-HFP.
Conclusion: In this study, PtCr promoted a more rapid and mature layer of ECs compared to PVDF-HFP which may be associated with the observation that a greater level of fibronectin is absorbed on PtCr. For PtCr, platelet adhesion and inflammatory cytokine secretion were favorable and comparable to PVDF-HFP, respectively. These data suggest that the luminal PtCr surface of the Synergy stent may provide an improvement in the re-endothelialization of DES compared to current conformal PVDF-HFP-coated stents, while maintaining acceptable levels of thromboresistance and inflammatory potential.

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Acute Effect of Percutaneous Renal Sympathetic Denervation on Renal Hemodynamics Using a Novel Radiofrequency Ablation Catheter in a Swine Model

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Background: Sympathetic overdrive is accompanied by impaired renal blood flow, whereas the effect of acute renal denervation on autoregulation of renal hemodynamics has yet to be elucidated. In this study we investigated whether renal sympathetic denervation, performed using a novel radiofrequency ablation catheter, might have an acute effect on renal hemodynamics assessed by average peak velocity (APV), renal flow reserve (RFR) and resistive index (RI).
Methods: We studied renal haemodynamics in 9 anaesthetized female juvenile farm swines (mean age 6 months, mean weight 34.5 kg). The renal angiogram percutaneously performed through femoral artery found no renal artery stenosis in all subjects. A 0.014-inch Doppler flow wire was introduced in the renal artery for the measurement of the APV under baseline and hyperemic condition that was induced by the bolus intrarenal administration of dopamine (50μg/kg). RFR was calculated as the ratio of hyperemic to basal peak velocity. RI was estimated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity. APV, RFR and RI were measured before and post renal sympathetic denervation. The sympathetic denervation was achieved via the lumen of the main renal artery with the novel catheter connected to a radiofrequency generator from St. Jude Medical according to pre-specified algorithm.
Results: In all animals, APV post ablation compared to APV before ablation was 300% higher (65.16±39.78 vs 21.79±8.53 cm/sec, p<0.0001). Radiofrequency ablation resulted in reduced RFR (1.51±0.59 vs 2.96±1.33, p<0.0001) and RI (0.66±0.07 vs 0.74±0.07, p=0.003), while no significant changes in the diameter of the renal artery was observed after dopamine administration (p=NS).
Conclusion: Catheter-based renal sympathetic denervation acutely augmented APV 3-fold, and significantly decreased RFR and RI in healthy swines. These results underscore the potent and acute effect of renal artery denervation by the radiofrequency ablation catheters on renal hemodynamic balance even in a healthy animal setting.

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Impact of the Different Route of Cell Delivery in Chronic Ischemic Cardiomyopathy Ovine Model

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Background: Bone marrow derived stem cells (BMDC) are currently used to treat patients with heart failure (HF) following myocardial infarction (MI). However, the optimal route for cell delivery is still controversial. In this study, we aimed to evaluate the effect of the route of cell delivery (direct surgical injection versus catheter-based transendocardial injection) in myocardial performance in an ovine model of ishemic cardiomyopathy.
Methods: Acute MI was induced by the percutaneous occlusion (90 min) of the left anterior descending artery via angioplasty balloon. At 4 wks after MI, 30 animals were randomized into one of the 4 groups: surgical control vehicle (n=5), surgical BMDC (n=5), trans-catheter vehicle (n=10) or trans-catheter BMDC (n=10). Stem cells (total 16 injections with 225 Million cells, 20 μL each,) or control vehicle were injected into the center and the border zone of infarct area via either an open chest surgical approach or catheter-based percutaneous delivery by experienced operators. Left ventricle performances were evaluated by echo prior and 8 wks following cell transplantation.
Results: At 4 wks after MI, all animals developed signs of HF characterized by reduced EF and dilated LV chamber. At 8 wks follow-up and compared to 4wks MI, ejection fraction (EF) was increased in both surgical (51±3% vs. baseline 45±3%, p<0.01) and trans-catheter (44±5% vs. baseline 41±5%, p<0.01) therapy groups. Compared to trans-catheter delivery, surgical delivery appeared to be more effective in decreasing LV end-systolic (ESV) and end-diastolic volume (EDV, Table).

	Vehicle			Cells		
Changes at 8wks FU from pre-therapy	Surgical	Trans-Catheter	P Value	Surgical	Trans-Catheter	P Value
ΔEDV (ml)	10±9	17±16	0.27	1±4	11±12	0.03
ΔESV (ml)	7±9	14±13	0.24	-3±2	5±7	0.01
ΔEF%	-4±6	-5±4	0.82	6±3	3±3	0.06

Conclusion: Both surgical and catheter-based deliveries of BMDC improve LV function in the chronic ischemic cardiomyopathy ovine model. However, surgical delivery appears to be more effective in reversing LV remodeling.

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Circadian Body Temperature Variability Corresponds to Significant Decline in Left Ventricular Function in Cardiomyopathic Hamsters

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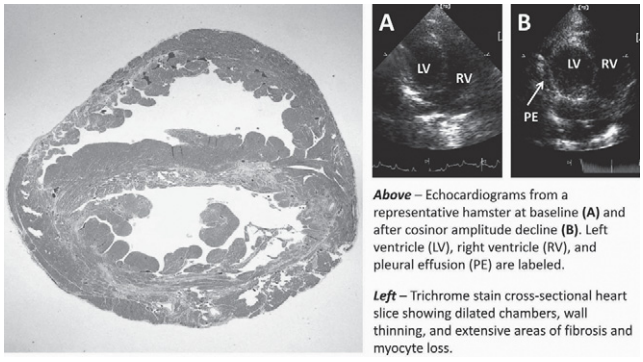
Background: Current methods of remotely monitoring patients with congestive heart failure (CHF) are inadequate. We tested the hypothesis that changes in body temperature circadian rhythm (BTCR) amplitude correspond with significant changes in left ventricular (LV) size and function.
Methods: We continuously monitored the temperature of 30 male BIO TO-2 cardiomyopathic hamsters with an intraperitoneal transmitter. Cosinor analysis was used to detect significant changes in each hamster's BTCR amplitude over the hamster's lifespan. Student's t test was used to examine changes in BTCR variability, as well as changes in left ventricular (LV) size and function as assessed by 2D echocardiography at baseline and when BTCR amplitude declined.
Results: At the time that each hamster's BTCR amplitude declined, functional parameters differed significantly (P<0.0001) from their baseline values: ejection fraction (0.31±0.09 vs 0.52±0.08), LV end-systolic volume (0.11±0.03 vs 0.05±0.02 cm3), and LV end-diastolic volume (0.16±0.04 vs 0.10±0.03 cm3). Histologic examination revealed features of advanced cardiomyopathy in all hearts; the fibrosis and mineralization from myocytes represented approximately 20% of the LV mass.



Above – Echocardiograms from a representative hamster at baseline **(A)** and after cosinor amplitude decline **(B)**. Left ventricle (LV), right ventricle (RV), and pleural effusion (PE) are labeled.

Left – Trichrome stain cross-sectional heart slice showing dilated chambers, wall thinning, and extensive areas of fibrosis and myocyte loss.

Conclusion: In decompensated cardiomyopathic hamsters, a significant decline in BTCR amplitude accompanied heart failure progression and cardiac decompensation. Therefore, BTCR may offer a simple yet effective means of remotely monitoring CHF progression and determining the timing of additional treatment.

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